18 **Shaer AJ**, Rastegar A. Lactic acidosis in the setting of antiretroviral therapy for the acquired immunodeficiency syndrome. *Am J Nephrol* 2000;**20**:332–8.
19 **Olano JP**, Borucki MJ, Wen JW, *et al*. Massive hepatic steatosis and lactic acidosis in a patient with AIDS who was receiving zidovudine. *Clin Infect Dis* 1995;**21**:973–6.
20 **Roy PM**, Gouello JP, Pennison-Besnier I, *et al*. Severe lactic acidosis induced by nucleoside analogues in an HIV-infected man. *Ann Emerg Med* 1999;**34**:282–4.
21 **Brivet FG**, Nion I, Mégarbane B, *et al*. Fatal lactic acidosis and liver steatosis associated with didanosine and stavudine treatment:a respiratory chain dysfunction? *J Hepatol* 2000;**32**:364–5.
22 **Chairot P**, Drogou I, Lacroix-Szmania I, *et al*. Zidovudine-induced mitochondrial disorder with massive liver steatosis, myopathy, lactic acidosis and mitochondrial DNA depletion. *J Hepatol* 1999;**30**:156–60
23 **Coyle T**, Abel E. Lactic acidosis and AIDS (letter). *Ann Intern Med* 1993;**19**:344.
24 **Freiman JP**, Helfert KE, Hamrell MR, *et al*. Hepatomegaly with severe steatosis in HIV-seropositive patients. *AIDS* 1993;**7**:379–85.
25 **Mégarbane B**, Brivet F, Guérin JM, *et al*. Acidose lactique et défaillance multi-viscérale secondaire aux thérapeutiques antirétrovirales chez les patients infectés par le VIH. *Press Med* 1999;**28**:2257–64.
26 **Falcó V**, Rodríguez D, Ribera E, *et al*. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis* 2002;**34**:838–46.
27 **Acosta BS**, Grimsley EW. Zidovudine-associated type B lactic acidosis and hepatic steatosis in an HIV-infected patient. *South Med J* 1999;**92**:421–3.
28 **Miller KD**, Cameron M, Wood LV, *et al*. Lactic acidosis and hepatic steatosis associated with use of stavudine: report of four cases. *Ann Intern Med* 2000;**133**:192–6.
29 **UNAIDS**. Aids epidemic update: December 2000. UNAIDS/ 00.44E-WHO/CSR/EDC/2000.9.
30 **Bozzette SA**, Berry SH, Duan N, *et al*. The care of HIV-infected adults in the United States. *N Engl J Med* 1998;**339**:1897–904.
31 **Scalfaro P**, Chesaux JJ, Buchwalder PA, *et al*. Severe transient neonatal lactic acidosis during prophylactic zidovudine treatment. *Intensive Care Med* 1998;**24**:247–50.
32 **Blanche S**, Tardieu M, Rustin P, *et al*. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999;**354**:1084–89.
33 **Lenzo NP**, Garas BA, French MA. Hepatic steatosis and lactic acidosis associated with stavudine treatment in an HIV patient:a case report. *AIDS* 1997;**11**:1294–6.
34 **Ter Hofstede HJM**, de Marie S, Foudraine NA, *et al*. Clinical features and risk factors of lactic acidosis following long-term antiretroviral therapy: 4 fatal cases. *Int J STD AIDS* 2000;**11**:611–6.
35 **Stenzel MS**, Carpenter CCJ. The management of the clinical complications of antiretroviral therapy. *Infect Dis Clin North Am* 2000;**14**:851–78.
36 **Carr A**, Miller J, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000;**14**:F25–32.
37 **Lonergan T**, Mccomsey G, Fisher R, *et al*. Improvements in symptomatic hyperlactatemia are observed after 12 weeks when stavudine is replaced by either abacavir or zidovudine. *3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*. Athens 2001 [abstract 81].
38 **White AJ**. Mitochondrial toxicity and HIV therapy. *Sex Transm Infect* 2001;**77**:158–73.
39 **Walker UA**, Stezer B, Venhoff N. Increased long-term mitochondrial toxicity in pyrimidine nucleoside combinations. *3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*. Athens 2001 [abstract 18].
40 **Bartley PB**, Westacott L, Boots RJ, *et al*. Large hepatic mitochondrial DNA deletions associated with L-lactic acidosis and highly active antiretroviral therapy. *AIDS* 2001;**15**:419–20.
41 **Miller RF**, Shahmanesh M, Hanna MG, *et al*. Polyphenotypic expression of mitochondrial toxicity caused by nucleoside reverse transcriptase inhibitors. *Antiviral Ther* (in press).
42 **Masini A**, Scotti C, Clligaro A, *et al*. Zidovudine-induced experimental myopathy: dual mechanism of mitochondrial damage. *J Neurol Sci* 1999;**166**:131–40.
43 **Leclercq P**, Roth H, Bosseray A, *et al*. Investigating lactate metabolism to estimate mitochondrial status. *3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*. Athens 2001 [abstract 21].
44 **Brinkman K**. Editorial response:hyperlactatemia and hepatic steatosis as features of mitochondrial toxicity of nucleoside analogue reverse transcriptase inhibitors. *Clin Infect Dis* 2000;**31**:167–9.
45 **Lafeuillade A**, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection. *Lancet* 2001;**357**:280–1.

ECHO

HAART homes in on lymphocyte mitochondria in lactic acidosis

Please visit the Sexually Transmitted Infections website [www.stijournal.com] for link to this full article.

A severe adverse reaction to highly active antiretroviral treatment (HAART) has shown for the first time the treatment's potential for damaging lymphocyte mitochondria and increasing lymphocyte death. This has prompted speculation that cell death follows mitochondrial disruption.

The case of severe lactic acidosis occurred in a 39 year old woman who had been HIV positive for nearly 10 years and receiving HAART with stavudine, didanosine, and indinavir for just over two and a half years. Viral load was <50 copies/ml and CD4+ lymphocytes >500 / ml. When treatment was stopped serum lactic acid concentration was about 5 mmol/l and γ-glutathione 14 times higher than normal. Acidosis started to decrease only one month afterwards and returned to normal only two months later. Mitochondria in the lymphocytes dropped in number and those remaining appeared swollen and their internal structure disrupted, with loss of christae. These traits persisted for a month after treatment was withdrawn, during which time apoptosis of CD3+ lymphocytes peaked. Apoptosis and mitochondrial abnormalities gradually resolved as lactic acid concentration dropped, and despite an increased viral load of 21 000 copies/ml. CD4+ lymphocyte numbers were unaffected.

Lymphocytes were typed by flow cytometry after staining with monoclonal antibodies. Apoptosis was measured by counting stained lymphocytes under fluorescence microscopy and by flow cytometry.

Lactic acidosis is a rare, but increasing, serious adverse reaction. This case provided a chance to see whether lymphocyte mitochondria are affected, given the importance of lymphocytes in HIV infection and reported mitochondrial damage in liver and skeletal muscle in similar cases.

▲ *Journal of Clinical Pathology* 2003;**56**:147–151.